REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 1-6 and 10-28 presently appear in the application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

The personal interview among Mr. Roger Browdy, Dr. Allen Yun, Dr. Steve Bossone and Ms. Jill Uhl, representing applicant, and Examiners Bo Peng, Jeffrey Stucker and James Housel on March 28, 2006, is gratefully acknowledged. Applicant's representatives wish to thank the examiners for the courtesies extended during this interview. While no agreement was reached on patentability, the examiners agreed that the amendments, arguments and declaration proposed and presented at the interview would be carefully considered when formally presented in a response. The arguments and amendments to the claims presented at the interview are incorporated herein.

The present specification at page 44, lines 19-24 cites specific U.S. patents for their disclosure of GHRH and GHRH analogs or agonists thereof which can stimulate the release of growth hormone. The disclosure in cited U.S. Patent 5,696,089 of the amino acid sequence of GHRH at the top of column 3, and truncated GHRH (fragments of GHRH) of residues 1-40 or 1-29 retaining the activity of stimulating the release of growth hormone has now been physically incorporated at the end of the paragraph on page 44, line 26, of the present specification. Note that these references were incorporated by reference in the

paragraph of the present specification beginning on page 51, line 4. Furthermore, in the paragraph beginning at page 43, line 25, the specification makes clear that these patents are being cited for their disclosure of GHRH and GHRH analogs or agonists. Thus, no new matter is being introduced by this physical incorporation of GHRH and fragments thereof. See MPEP §608.01(p). The 44 residue amino acid sequence of GHRH presented at the top of column 3 of U.S. Patent 5,696,089 is physically incorporated and now presented in the instant application as SEQ ID NO:1 in the sequence listing attached hereto.

Applicants have added into the present specification a new paper copy Sequence Listing section according to 37 C.F.R. §1.821(c) as new sequence listing page 1. Furthermore, attached hereto is a 3 1/2" disk containing the "Sequence Listing" in computer readable form in accordance with 37 C.F.R. §1.821(e).

Applicants have amended the specification to insert this new SEQ ID NO, as supported in the present specification.

The following statement is provided to meet the requirements of 37 C.F.R. §1.821(f) and 1.821(g).

I hereby state, in accordance with 37 C.F.R. §1.821(f), that the content of the attached paper and computer readable copies of the sequence listing are believed to be the same.

I hereby also state, in accordance with 37 C.F.R. §1.821(g), that the submission is not believed to include new matter.

Appropriate correction to the status of application no. 09/475,989 as being "now issued as U.S. Patent 6,696,063" is made to the first sentence of the specification.

The disclosure has been objected to because it contains an embedded hyperlink and/or other form of browser-executable code. This objection is respectfully traversed.

MPEP §608.01 VII states that examples of a hyperlink as a browser-executable code prohibited by 37 C.F.R. §1.57(d) are "a URL placed between these symbols '< >' and http:// followed by a URL address." The URL address on page 55 is not a hyperlink, nor is it browser-executable, as "http://" is not present and the symbols "< >" are not used. URL's, such as at page 55, are permissible. Only hyperlinks and browser-executable codes are prohibited. As the URL on page 55 is neither, reconsideration and withdrawal of this objection is respectfully urged.

Claims 1-9 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is obviated by the cancellation of claims 7-9 without prejudice to the refiling in a continuation application and the amendment to claim 1 to positively recite that the fragment, variant, analog, derivative or salt of hGHRH retains the ability to stimulate the release of growth hormone.

Although the definitions of "fragments" (page 35, lines 9-18) "variants or analogs" (pages 36-38 and 41-43), "functional

derivatives" (page 33, line 10, to page 34, line 20; page 38, line 23, to page 40, line 16) and "salts" (page 34, line 21, to page 35, line 8) are provided in the specification with respect to retaining the biological activity of hGH, it is clear from the later disclosure on page 44, lines 5-19, that such definitions also apply to fragments, variants, analogs, functional derivatives and salts of hGHRH, except that the biological activity retained is the ability to stimulate the release of growth hormone.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Claims 1-9 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The examiner states that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The examiner takes the position that, to provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus, and factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, structure/function correlation, methods of making the

claimed product, or any combination thereof. This rejection is respectfully traversed.

At the personal interview, applicant's representatives reminded Examiner Housel that in the parent application, which issued as U.S. Patent 6,696,063, he and Examiner Foley had approved claims to functional derivatives, fragments, variants, analogs or salts of human growth hormone which retained the biological activity of human growth hormone because applicant was claiming a method of use and not a novel protein and because the art was aware of many fragments, variants, analogs and functional derivatives of human growth hormone. The same should apply here with regard to human growth hormone releasing hormone (hGHRH), which stimulates the release of human growth hormone, because the present specification at page 44, lines 19-26, cites a representative listing of U.S. patents and publications which disclose and teach numerous hGHRH fragments, variants, analogs and functional derivatives that retain the ability to stimulate the release of growth hormone.

U.S. Patent 5,696,089 (Felix et al.), cited on page 44 and listed as Ref. AQ in an IDS Form 1449 initialed by the examiner, discloses at column 2, lines 25-45, fragments, variants, analogs and functional derivatives of hGHRH (also known as hGRF) with the formula:

1 5 10

R_1-R_2-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-

15 20 (I)
Arg-Lys-Val-Leu-R_3-Gln-Leu-Ser-Ala-Arg-

25
Lys-Leu-Leu-Gln-Asp-Ile-R_4-R_5-R_6-X

Depending on the length of R_6, which corresponds to one or more residues starting from residue 30 to 44 of hGHRH (of SEQ ID NO:1), the compound of formula (I) ranges from 29 to 44 residues in length and represents either an analog/variant of hGHRH or an analog/variant of an hGHRH fragment where the fragment is C-terminally truncated at a position between residue 29 and 44 of hGHRH. Certain identified amino acid substitutions can be made at six specific residue positions (1, 2, 15, 27, 28, and 29) for a sequence identity of at least 80% (6 residue changes per minimum 29 residues) with native hGHRH or corresponding fragments thereof. Eleven specific representative analogs/variants of hGHRH are presented at column 4, lines 42-54, with the potency of four of the analogs relative to hGHRH (1-44)-NH_2 being shown in Table 1 at column 14. As can be seen in Table 1, the analogs tested retain the ability to stimulate the release of growth hormone.

U.S. Patent 5,846,936 (Felix et al.), cited on page 44 and listed as IDS Ref. BM, discloses at column 2, lines 40-55, analogs similar to those disclosed in U.S. Patent 5,696,089

discussed above, but with more alternative residues at residue position 2 and an additional residue (residue position 8) where certain identified amino acid substitutions can be made. The length of these analogs ranges from 29 to 44 residues for a sequence identity of at least 76% (maximum 7 residue changes per minimum 29 residues) with native hGHRH or corresponding fragments thereof. Column 4, line 51, to column 5, line 10, provides a list of 19 specific representative analogs/variants of hGHRH and column 16, Table 1, shows the potency of 9 different analogs relative to hGHRH (1-44)-NH_2, where all 9 analogs retain the ability to stimulate the release of growth hormone.

U.S. Patent 5,137,872 (Seely et al.), cited on page 44 and listed as IDS Ref. AI, discloses in the background section on prior art references that fragments of hGF (hGHRH), e.g., hGHRH (1-27)-NH_2, hGHRH (1-29)-NH_2, and hGHRH (1-40)-NH_2, exhibited similar activity to the parent hGHRH (1-40)-OH peptide. Column 2, line 2, to column 3, line 8, further discloses extensive prior art fragments, analogs/variants and N-terminally modified hGHRH ("functional derivative"). This Seely et al. reference teaches analogs of hGHRH (1-29)-NH_2 to (1-44)-NH_2, where a Pro residue is added to the N-terminus, residue position 15 of hGHRH is Ala or Gly and residue position 27 is Ile, Leu, Val, Nle or Met, with [Pro^0, Gly^{15}, Met^{27}]-hGHRH (1-44)-NH_2 being the preferred analog embodiment.

U.S. Patent 5,847,066 (Coy et al.), cited on page 44 and listed as IDS Ref. BN, discloses (abstract; column 1, line 45, to column 2 line 24) hGHRH analogs/variants of 23-28 residues in length which differ from native hGHRH at least at residue positions 8, 9, 16, 18, 24, 25, 27 and 28 with also possible changes at residue positions 1, 2, 10, 12, 15, 16, 21, 23 and 26. A number of chemical modifications (derivatives) at least at residue positions 1, 2, 10, 12, 21 and 28 are also taught. Coy further teaches 26 representative examples of specific analogs at column 2, line 25, to column 6, line 16, with the potency of growth hormone release relative to hGHRH (1-26)-NH_2 shown in Table 1 (column 12) for all 26 analogs. It is clear from Table 1 that all 26 analogs retain the ability to stimulate the release of growth hormone.

U.S. Patent 5,792,747 (Schally et al.), cited on page 44 and listed as IDS ref. BE, discloses at column 2, line 61, to column 3, line 67, 28 residue analogs of hGHRH with amino acid changes at most at residue positions 1, 2, 3, 8, 12, 13, 15, 21, 22, 23, 25, 27 and 28 of hGHRH (1-28) for a minimum sequence identity of approximately 54% (maximum 13 residue changes per 28 residues). A number of chemical modifications is also taught. Column 6, lines 1-51, discloses four specific representative examples of preferred embodiments of hGHRH analogs, where the potency of the analogs is presented at columns 16-18, Examples IX

and X, Tables 1-3. All four analogs tested retain the ability to stimulate the release of growth hormone.

U.S. Patent 5,861,379 (Ibea et al.), listed as Ref. EX in the IDS filed even date herewith, discloses fatty body analogs of hGHRH, such as a preferred N-hexenoyl (C_6) tail anchored at the N-terminus of hGHRH (1-29)-NH_2, which retain the ability to stimulate the release of growth hormone (Examples III and IV, columns 17-20).

The disclosures and teachings of fragments, analogs/variants, and functional chemical derivatives of hGHRH in the prior art are certainly extensive, although it should be noted that the above cited U.S. patents are by no means an exhaustive list of prior art references with disclosures of hGHRH analogs/variants, fragments and functional chemical derivatives.

Clearly, in the same manner that the examiners in the parent application (which issued as U.S. Patent 6,696,063) found human growth hormone analogs/variants, fragments, functional derivatives and salts, to have adequate written description in the present specification, the examiners should find the presently recited hGHRH analogs/variants, fragments, functional derivatives and salts to also have adequate written description in the present specification.

In the above cited U.S. patents, examples of functional chemical derivatives are disclosed that are encompassed by the

functional derivative defined in the present specification (i.e., at page 33, line 10, to page 34, line 20; page 38, line 23, to page 40, line 16), which are only intended to include those derivatives that are modified at side chains of the amino acid residues or at the N- or C-terminal groups of the peptide and that do not change one amino acid to another of the twenty commonly-occurring natural amino acids (page 34, lines 18-20).

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Before discussing the prior art rejections individually, applicant wishes to emphasize that the parent application was allowed because it was recognized by the examiner that there is a distinction between HIV (AIDS wasting) and HIV-associated dysmorphia/dysmetabolic syndrome (HADDS), also known as HIV-associated adipose redistribution syndrome (HARS), and also that there is a distinction between obesity and HADDS. The same issue appears in the instant prior art rejections.

Claims 1-9 have been rejected under 35 U.S.C. §102(b) as being anticipated by Wilson et al., *Metabolism, Clinical and Experimental* 45(6):738-746 (1996). The examiner states that Wilson teaches administering hGHRH to HIV-infected individuals and that, although Wilson does not mention "HADDS" or diminishment of redistributed fat, the patient population, method steps and ingredients administered by Wilson are

indistinguishable from those instantly claimed. The examiner concludes that diminishment of redistributed fat in HIV-infected individuals is an inherent property of hGHRH. This rejection is respectfully traversed.

Wilson studied the endocrine status of HIV-infected individuals by administering rGHRH and determining the level of induction of growth hormone by rGHRH in HIV-infected patients. Contrary to the examiner's assertion, the patient population with HADDS is very different from the patient population of HIV-infected individuals. The present specification teaches at page 17, lines 5-9:

> Metabolic abnormalities do not occur in every patient with HADDS, and not every HIV patient who develops metabolic abnormalities (while receiving protease inhibitors, other antiretroviral agents, or receiving no agents at all) concurrently develops abnormal fat accumulation. (emphasis added)

Thus, HADDS is found in a subset of HIV patients who develop metabolic abnormalities, which in turn is a subset of all HIV patients. Accordingly, HADDS occurs in only a small subset (approximately 10%) of HIV patients. In *Ex parte Cyba*, 155 USPQ 757, the Board held that "In order that a rejection based upon inherency may be sustained such inherency must be certain" (emphasis added). However, the examiner has already acknowledged that Wilson does not mention "HADDS" (or, for that matter, any of the characteristics of HADDS). Therefore, there can be no

inherency and Wilson cannot anticipate the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-9 have been rejected under 35 U.S.C. §102(b) as being anticipated by Draper et al., U.S. Patent 5,767,124. The examiner states that Draper anticipates administering growth hormone secretagogues to obese and HIV-infected individuals. The examiner further states that although Draper does not mention "HADDS" or diminishment of redistributed fat, the method steps, population and ingredients administered are indistinguishable from those instantly claimed. This rejection is respectfully traversed.

With regard to HIV-infected individuals, Draper cannot anticipate the presently claimed invention for the same reasons as discussed above with respect to the anticipation rejection over Wilson. With regard to Draper's disclosure of administering a growth hormone secretagogue to obese individuals, the arguments and evidence presented in parent application 09/475,989 to distinguish HADDS from obesity and therefore to distinguish the patient population are particularly relevant and repeated in part below.

Attached hereto are pertinent pages from STEDMAN's MEDICAL DICTIONARY, 26th Edition, 1995, Williams & Wilkins,

Baltimore, MD, with definitions of "obesity" and "lipodystrophy". "Obesity" is defined as an abnormal increase of fat in subcutaneous connective tissue, whereas "lipodystrophy" is defined as a defective metabolism of fat.

Also attached hereto is a copy of a declaration under 37 CFR §1.132 executed by Dr. Ramon TORRES, which was submitted in parent application 09/475,989. This declaration provides statements and evidence (i.e., Exhibit B) regarding the distinction between HADDS and obesity. It is quite clear to those of skill in the art that treating obesity, the subject of the applied Draper reference, is different from treating HADDS. Accordingly, Draper cannot anticipate the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 7-9 have been rejected under 35 U.S.C. §102(b) as being anticipated by Mugica, U.S. Patent 5,120,713, or Bowers et al., U.S. Patent 5,663,146. The examiner holds that Mugica or Bowers anticipates administering hGHRH or derivatives to obese individuals to diminish fat tissue. This rejection is obviated by the cancellation of claims 7-9 without prejudice.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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